Agency for Healthcare Research and Quality
Advancing Excellence in Health Care

NATIONAL GUIDELINE CLEARINGHOUSE

General

Guideline Title

Omalizumab for treating severe persistent allergic asthma (review of technology appraisal guidance 133 and 201).

Bibliographic Source(s)

National Institute for Health and Care Excellence (NICE). Omalizumab for treating severe persistent allergic asthma (review of technology appraisal guidance 133 and 201). London (UK): National Institute for Health and Care Excellence (NICE); 2013 Apr. 64 p. (Technology appraisal guidance; no. 278).

Guideline Status

This is the current release of the guideline.

This guideline updates two previous versions:

- National Institute for Health and Clinical Excellence (NICE). Omalizumab for the treatment of severe persistent allergic asthma in children aged 6 to 11 years. London (UK): National Institute for Health and Clinical Excellence (NICE); 2010 Oct. 38 p. (Technology appraisal guidance; no. 201).
- National Institute for Health and Clinical Excellence (NICE). Omalizumab for severe persistent allergic asthma. London (UK): National Institute for Health and Clinical Excellence (NICE); 2007 Nov. 28 p. (Technology appraisal guidance; no. 133).

Regulatory Alert

FDA Warning/Regulatory Alert

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- September 26, 2014 – Xolair (omalizumab) : A U.S. Food and Drug Administration (FDA) review of safety studies suggests a slightly increased risk of problems involving the heart and blood vessels supplying the brain among patients being treated with the asthma drug Xolair (omalizumab) than in those who were not treated with Xolair. As a result, FDA has added information about these potential risks to the drug label.

Recommendations

Major Recommendations

Major Recommendations

Omalizumab is recommended as an option for treating severe persistent confirmed allergic immunoglobulin E (IgE)-mediated asthma as an add-on to optimised standard therapy in people aged 6 years and older:

- Who need continuous or frequent treatment with oral corticosteroids (defined as 4 or more courses in the previous year), and
- Only if the manufacturer makes omalizumab available with the discount agreed in the patient access scheme.

Optimised standard therapy is defined as a full trial of and, if tolerated, documented compliance with inhaled high-dose corticosteroids, long-acting beta$_2$ agonists, leukotriene receptor antagonists, theophyllines, oral corticosteroids, and smoking cessation if clinically appropriate.

People currently receiving omalizumab whose disease does not meet the criteria in the first recommendation above should be able to continue treatment until they and their clinician consider it appropriate to stop.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Severe persistent allergic asthma

Guideline Category

Assessment of Therapeutic Effectiveness

Treatment

Clinical Specialty

Allergy and Immunology

Family Practice

Internal Medicine

Pediatrics

Pulmonary Medicine

Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To determine the clinical effectiveness, safety, and cost-effectiveness of omalizumab in adults and adolescents aged at least 12 years and in children aged six to 12 years

Target Population

Adults and adolescents aged at least 12 years and children aged six to 12 years with severe persistent allergic asthma

Interventions and Practices Considered

Omalizumab as an add-on to optimised standard therapy

Major Outcomes Considered

- Clinical effectiveness
  - Asthma symptoms
  - Incidence of exacerbations (clinically significant exacerbations and severe exacerbations)
  - Hospitalisations due to asthma-related incidents
  - Mortality, use of oral corticosteroids (reduction in dose or frequency or withdrawal)
  - Time to discontinuation of treatment
  - Adverse effects of treatment
  - Health-related quality of life
  - Adverse events associated with omalizumab, namely: malignancies, anaphylaxis, arterial thrombotic events, and mortality
  - Adverse effects of oral corticosteroids, including: bone outcomes (such as fracture), incidence of infectious disease, hypertension, ocular outcomes including cataracts and glaucoma and, in children and adolescents, growth retardation
- Cost-effectiveness

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Care Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an assessment report. The assessment report for this technology appraisal was prepared by the Centre for Reviews and Dissemination (CRD) and the Centre for Health Economics (CHE) (see the "Availability of Companion Documents" field).

Assessment of Clinical Effectiveness

Methods for Reviewing Clinical Effectiveness

The review of clinical effectiveness addressed five distinct questions: the efficacy of omalizumab; the long-term efficacy of omalizumab; the steroid sparing effect of omalizumab; the safety of omalizumab; and the adverse effects of oral corticosteroids (OCS). The conduct of full systematic reviews of the evidence to address all five questions was neither warranted nor possible within the limited time available for the review. The methods used are detailed by question below. The review was conducted following the general principles published in CRD's guidance for conducting systematic reviews and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

Methods for Reviewing the Efficacy of Omalizumab (Including Long-term Outcomes and Steroid Sparing)

Search Strategy

Studies relevant to an assessment of the therapeutic effect of omalizumab were identified by searching the following databases: MEDLINE, MEDLINE In-Process, EMBASE, Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effects (DARE), and Health Technology Assessment Database (HTA), the National Institutes of Health (NIH) ClinicalTrials.gov Register, Current Controlled Trials, Conference Proceedings Citation Index (CPCI-S), and EconLit. Searches were run in September 2011 and re-run in October 2011 following the identification of an additional search term at the screening stage of the review. Full details of the search strategy are provided in Appendix 12.1 of the Assessment Report. Additional searches of trial registers, journals, and reference lists of relevant published systematic reviews were conducted to identify any further studies of relevance. No limits on date, language, or study design were applied. Endnote software was used to download and import references and remove duplicates. The submissions provided to NICE by Novartis and the associated documents were also used as sources of relevant studies for the review.

Study Selection

Abstracts of identified studies and potentially relevant full papers were independently assessed for inclusion in the review by two reviewers using the criteria outlined below. Disagreements were resolved through discussion and, where necessary, by consultation with a third reviewer.

Intervention

The intervention of interest was omalizumab given parenterally as a subcutaneous injection every two to four weeks depending on dose in addition to best standard therapy at step 4 or step 5 of the Global Initiative for Asthma (GINA) treatment guideline (the dose and frequency of administration of omalizumab are determined by baseline immunoglobulin E [IgE] measured before the start of treatment, and body weight).

Comparators

The direct comparator considered was optimised standard therapy. Standard therapy was step 4 or step 5 (GINA guideline) treatment. Optimisation of standard therapy was considered to include the elimination of modifiable factors in addition to treatment compliance. The following comparators were considered:

In adults and children:

i. Daily high-dose inhaled corticosteroids (ICS) plus a long-acting $beta_2$-agonists (LABA) with the possible addition of leukotriene receptor antagonist, theophyllines, or slow releasing $beta_2$-agonist tablets (GINA Step 4).
ii. Daily high-dose ICS plus a LABA with the possible addition of leukotriene receptor antagonist, theophyllines, or slow releasing $beta_2$-agonist tablets plus frequent or continuous OCS (GINA Step 5).

After finalisation of the review protocol it was established that methotrexate, ciclosporin, and gold were not considered appropriate treatment for adults or children at Step 4 or step 5 (GINA guideline) and therefore these treatments were not included as comparators in the review.

Participants

Studies in which the whole population, or a clearly defined sub-group of the population, or a large proportion of the population, met the following criteria (which reflect the UK licence for omalizumab) were eligible for inclusion in the review: adults and adolescents aged at least 12 years with severe persistent allergic asthma and:

i. A positive skin test or in vitro reactivity to a perennial aeroallergen
ii. Reduced lung function (forced expiratory volume in one second [FEV_1] <80%)
iii. Frequent daytime symptoms or night-time awakenings
iv. Multiple documented severe asthma exacerbations despite daily high-dose ICS plus a long-acting inhaled $beta_2$-agonist

or children aged between six and 12 years with severe persistent allergic asthma and:

i. A positive skin test or in vitro reactivity to a perennial aeroallergen
ii. Frequent daytime symptoms or night-time awakenings
iii. Multiple documented severe asthma exacerbations despite daily high-dose ICS plus a long-acting inhaled $beta_2$-agonist.

To address the question of the steroid sparing effect of omalizumab, for which it was anticipated evidence would be sparse, studies whose

populations did not meet these criteria were included.

Outcomes

Studies that reported the following outcomes were eligible for the review: asthma symptoms, incidence of exacerbations (clinically significant exacerbations and severe exacerbations), hospitalisations due to asthma-related incidents, mortality, use of OCS (reduction in dose or frequency or withdrawal), time to discontinuation of treatment, adverse effects of treatment, and health related quality of life.

Study Designs

Randomised controlled trials (RCTs) with a comparator of placebo, standard care, or another active intervention were eligible for the review. Data from quasi-RCTs and observational studies were also considered in order to provide supporting evidence and in particular, data on longer term response and adherence to treatment and steroid sparing. These included open-label continuation studies, non-comparative cohort studies and post-marketing studies (to include ≥30 patients or long term data [≥2 years]).

Methods for Reviewing the Safety of Omalizumab

Search Strategy

In addition to the searches conducted for the review of the efficacy of omalizumab information on adverse events of omalizumab were identified from searching resources of the US and European drug regulatory agencies (US Food and Drug Administration [FDA] and European Medicines Agency [EMA]). No language or date restrictions were applied to the search strategy. In addition, reference lists of all included studies and industry submissions made to NICE were hand-searched to identify further relevant studies.

Inclusion and Exclusion Criteria

Documents and studies on the adverse effects of omalizumab were relevant for the review. The lists of titles/abstracts generated by the electronic searches and all full paper manuscripts and documents of possible relevance to the review of safety of omalizumab were obtained where possible and the relevance of each study was assessed by two reviewers; any discrepancies were resolved by consensus. Potentially relevant studies that did not meet all of the criteria were excluded and their bibliographic details listed with reasons for exclusion.

Study Design

RCTs (including any open-label extensions of these RCTs) and observational studies (including post-marketing surveillance) were included in the evaluation of safety. Information on the rate of adverse events was sought from regulatory sources (FDA, EMA). Previously published reviews were also included where their main aim was the safety of omalizumab.

Outcomes

A general overview of the adverse effects of omalizumab was obtained from previous reviews and regulatory agencies' documents. The review of primary studies specifically focused on the adverse events of particular concern associated with omalizumab, namely: malignancies, anaphylaxis, arterial thrombotic events, and mortality. In addition, data relating to the most commonly reported adverse events were also considered. On-going long-term safety studies were also identified and discussed briefly.

Methods for Reviewing the Adverse Effects of OCS

Search Strategy

The review team were given access to an existing internal CRD database of systematic reviews of adverse events. This database was searched using the terms steroid, corticosteroid, glucocorticoid, and all individual steroid names. This search was supplemented by a search of the Cochrane library and DARE using terms for steroids coupled with terms for asthma. A further supplementary search was conducted on PubMed to try to identify any very recent relevant systematic reviews.

Inclusion and Exclusion Criteria

Any review of the adverse effects of OCS were considered for inclusion in the review. The steroid-related adverse events of particular interest included: bone outcomes (such as fracture), incidence of infectious disease, hypertension, ocular outcomes including cataracts and glaucoma and, in children and adolescents, growth retardation.

Systematic Review of Existing Cost-Effectiveness Evidence

Methods

Systematic searches of the literature were conducted to identify potentially relevant studies for inclusion in the assessment of cost-effectiveness of omalizumab against any comparator. Full economic evaluations that compared two or more options and considered both costs and consequences (including cost-effectiveness, cost-utility, and cost-benefit analyses) were included. Full details of the search strategies are reported in Appendix 12.1 of the Assessment Report. Titles and abstracts were assessed independently by two reviewers for inclusion and any discrepancies were resolved by consensus.

Number of Source Documents

Clinical Effectiveness

73 publications were included in review of omalizumab efficacy: 11 randomised controlled trials with 40 supporting publications; and 11 observational studies with 11 supporting publications.

Cost-Effectiveness

- Six studies were included in the cost-effectiveness review.
- The manufacturer submitted an economic model.

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Care Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an assessment report. The assessment report for this technology appraisal was prepared by the Centre for Reviews and Dissemination (CRD) and the Centre for Health Economics (CHE) (see the "Availability of Companion Documents" field).

Assessment of Clinical Effectiveness

Methods for Reviewing the Efficacy of Omalizumab (Including Long-term Outcomes and Steroid Sparing)

Data Extraction

Data relating to both study design and quality were extracted by one reviewer using a standardised data extraction form and independently checked for accuracy by a second reviewer. Disagreements were resolved through consensus, and if necessary, a third reviewer was consulted. Attempts were made where possible to contact authors and study sponsors for missing data. Data from studies with multiple publications were extracted and reported as a single study. Additional data were also extracted from the manufacturer's submission; where this is the case the trial publications are not referenced.

Quality Assessment

The quality of randomised controlled trials (RCTs) was assessed using standard checklists following the principles of CRD. The original protocol was amended to also include the assessment of risk of bias following the principles of the Cochrane Collaboration. For non-randomised studies,

tools based on CRD guidance were used. Quality assessment was performed by one reviewer, and independently checked by a second.

Data Analysis

Outcomes

Data were presented separately for each outcome reported. Some trials divided the primary review outcome of clinically significant exacerbations into clinically significant severe (CSS) exacerbations and clinically significant non-severe (CSNS) exacerbations. Therefore an outcome of 'total exacerbations' is reported which includes all exacerbations reported as clinically significant from all trials. CSS and CSNS exacerbations where reported were also analysed separately. Where possible, data on each component of unscheduled health care use (hospitalisation, emergency room attendance, and unscheduled doctor appointments) were analysed separately; in cases where only composite outcomes were reported this was noted. Asthma symptom scores, quality of life, and incidence of particular symptom measures were summarised where possible given the heterogeneity in assessment methods. Where appropriate and where data were available, study estimates of the effect of omalizumab (relative risks, risk, ratios, mean differences, with 95% confidence intervals) were calculated.

Main Review of Efficacy: Randomised Controlled Trials

Data from RCTs were considered separately from those from observational studies. RCTs enrolling adults and children were considered separately throughout. In both adults and children a distinction was drawn between included trials which included only patients who met the licence criteria, those in which a defined subgroup met or closely approximated the licence criteria and those which were included as supportive evidence in which an undefined proportion of the trial population met the licence criteria, but where these individuals were not an identified subgroup. In all analyses data are reported for the whole trial population where this corresponded to the licensed population; where a defined subgroup of the trial population met the licence criteria the analyses used the data for that subgroup. For supportive trials in which licensed subgroups were not defined, data for the whole trial were reported with the caveat that patients outside the licensed population contributed to the estimates of effect.

Approach to Synthesis

Whilst a statistical synthesis (meta-analysis) of the results of the identified RCTs was planned, in practice this was not appropriate for any analysis due to significant clinical heterogeneity amongst the trials of adult patients. In the case of children there was only one trial in which a defined subgroup met the licence criteria and one further trial was included as supportive evidence. Therefore a narrative synthesis of results was clearly appropriate. Intention to treat (ITT) data were used where possible, where this was not possible, the fact was noted. For responder analyses response rates were calculated using the total number of patients randomised. Rate ratios were reported for the outcomes of exacerbations and relative risks for outcomes of hospitalisation and other unscheduled care use. Mean differences were reported where possible for outcomes of quality of life and asthma symptoms.

Pooled estimates for rate ratios combining data from two main trials are presented in tables of data on total clinically significant exacerbations, clinically significant severe exacerbations and clinically significant non-severe exacerbations only because these formed the basis for sensitivity analyses in the economic model. These were calculated using an inverse variance fixed effect model.

Responder Analyses

Efficacy in the responder population (patients showing improvements in asthma symptoms with omalizumab treatment at 16 weeks) is of key importance to the assessment of both clinical and cost- effectiveness. Therefore, in addition to an ITT analysis, detailed consideration was given to the analyses comparing omalizumab responders with control patients where these were reported. Data derived from differing definitions of response rate were not considered for pooling. As with the ITT analyses, where a meta-analysis was not appropriate a narrative synthesis supported by detailed evidence tables was conducted. Again, pooled estimates of data from two main trials are presented only because of their use in sensitivity analyses for the economic model.

Subgroups

In addition to the a priori subgroups defined as meeting the licence criteria which were discussed above, analyses of the following pre-specified subgroups were undertaken where sufficient data were available. These included:

i. Subgroups defined by the degree of poor asthma control in terms of number, type, and severity of exacerbations, including hospitalisation for an asthma exacerbation (adults and children)
ii. Subgroups defined according to concomitant treatment received such as maintenance OCS (adults only)

These subgroups were explored in the ITT analyses and the responder analyses. The subgroup data were derived from the manufacturer's submission and from additional information supplied by the manufacturer in response to a request from the assessment group and represented

post-hoc subgroups which comprised small numbers of patients. The methodological heterogeneity between the trials.

Methods for Reviewing the Safety of Omalizumab

Data relating to adverse and serious adverse events were extracted using a standardised data extraction form and the quality of RCTs and other study designs were assessed using standard checklists. Reviews and regulatory documents were not formally quality assessed. Data extraction and quality assessment was performed by one reviewer and independently checked for accuracy by a second reviewer. Disagreements were resolved through consensus. No formal analysis of the data was performed; the adverse effects of omalizumab were presented as a narrative synthesis.

Methods for Reviewing the Adverse Effects of OCS

Relevant data were extracted by one reviewer and checked by a second. The quality of the included reviews was discussed but not formally assessed. The findings of the included reviews were combined in a narrative synthesis.

Assessment of Existing Cost-Effectiveness Evidence

Systematic Review of Existing Cost-Effectiveness Evidence

Data were extracted by one reviewer using a standardised data extraction form and checked for accuracy by a second reviewer. The quality of these studies was assessed according to a general checklist together with a more specific checklist for decision models. This information is summarised within the text of the Assessment Report, alongside a detailed critique of the main studies and their relevance to the UK National Health Service (NHS). The findings from the review provide the basis for the development of a new model (see below).

The manufacturer (Novartis UK) also submitted *de novo* evidence on the cost-effectiveness of omalizumab for severe persistent allergic asthma for the present evaluation of omalizumab. The manufacturer's submission is reviewed in Section 6.3 of the Assessment Report, alongside a detailed critique.

A review of existing cost-effectiveness evidence was also undertaken by the manufacturer. Their aim was to identify full economic evaluations of omalizumab in the specific patient population corresponding to the UK/EU marketing authorisation of omalizumab. The manufacturer's review excluded studies of patients younger than 6 years, and studies including patients with mild, moderate, acute, or intermittent asthma, or conditions other than asthma. Therefore, the inclusion criteria for the manufacturer's systematic review were stricter than the review presented in the Assessment Report. The studies included in the manufacturer's review were examined and compared to those found in the review presented in the Assessment Report.

For additional information on the manufacturer's *de novo* submission, see Section 6.3 of the Assessment Report.

Previous NICE Single Technology Appraisals

Omalizumab has been the subject of two single technology assessments (STAs) for NICE; TA133 in adults and adolescents (12 years and older), and TA201 in children aged 6 to 11 years. As part of these previous STAs, evidence was submitted by the manufacturer and a review of the submission was undertaken by a separate Evidence Review Group (ERG). In Section 6.2 in the Assessment Report, each STA is briefly reviewed separately, and an overall critique is presented at the end.

Assessment of Cost-Effectiveness: York Economic Assessment

A decision analytic model was developed to formally assess the cost-effectiveness of omalizumab as an add-on therapy to optimised standard care compared with optimised standard care alone from the perspective of the UK NHS. Outcomes are expressed in terms of quality-adjusted life years (QALYs). Costs are expressed in UK pound sterling at a 2009/10 price base. Both costs and outcomes are evaluated over a lifetime and discounted using a 3.5% annual discounted rate, according to the NICE reference case. See Section 7 of the Assessment Report for additional details.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Considerations

Technology appraisal recommendations are based on a review of clinical and economic evidence.

Technology Appraisal Process

The National Institute for Health and Care Excellence (NICE) invites 'consultee' and 'commentator' organisations to take part in the appraisal process. Consultee organisations include national groups representing patients and carers, the bodies representing health professionals, and the manufacturers of the technology under review. Consultees are invited to submit evidence during the appraisal and to comment on the appraisal documents.

Commentator organisations include manufacturers of the products with which the technology is being compared, the National Health Service (NHS) Quality Improvement Scotland and research groups working in the area. They can comment on the evidence and other documents but are not asked to submit evidence themselves.

NICE then commissions an independent academic centre to review published evidence on the technology and prepare an 'assessment report'. Consultees and commentators are invited to comment on the report. The assessment report and the comments on it are then drawn together in a document called the evaluation report.

An independent Appraisal Committee then considers the evaluation report. It holds a meeting where it hears direct, spoken evidence from nominated clinical experts, patients and carers. The Committee uses all the evidence to make its first recommendations, in a document called the 'appraisal consultation document' (ACD). NICE sends all the consultees and commentators a copy of this document and posts it on the NICE Web site. Further comments are invited from everyone taking part.

When the Committee meets again it considers any comments submitted on the ACD; then it prepares its final recommendations in a document called the 'final appraisal determination' (FAD). This is submitted to NICE for approval.

Consultees have a chance to appeal against the final recommendations in the FAD. If there are no appeals, the final recommendations become the basis of the guidance that NICE issues.

Who Is on the Appraisal Committee?

NICE technology appraisal recommendations are prepared by an independent committee. This includes health professionals working in the NHS and people who are familiar with the issues affecting patients and carers. Although the Appraisal Committee seeks the views of organisations representing health professionals, patients, carers, manufacturers and government, its advice is independent of any vested interests.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

Summary of Appraisal Committee's Key Conclusions on Cost-Effectiveness

Availability and Nature of Evidence

There were no specific conclusions made by the Committee about the availability and nature of the cost-effectiveness evidence.

Uncertainties Around and Plausibility of Assumptions and Inputs in the Economic Model

The Committee noted that the main differences between the manufacturer's and the Assessment Group's economic models were the assumptions on asthma-related mortality and how health-related quality of life improvements from omalizumab treatment were incorporated in the models. The Committee concluded that considerable uncertainty remained about the asthma-related mortality associated with severe persistent asthma, and that two studies used in the model may not reflect mortality among the subgroups of people with very severe persistent asthma, to whom omalizumab is offered in clinical practice.

Incorporation of Health-Related Quality-of-Life Benefits and Utility Values

The Committee preferred the Assessment Group's approach in which the same utility gain was assumed for adults, adolescents, and children.

The Committee preferred the Assessment Group's method of using direct estimates of EQ-5D values, in line with the National Institute for Health

and Care Excellence (NICE) reference case, to the manufacturer's approach of mapping Asthma Quality of Life Questionnaire scores collected in the INNOVATE trial onto EQ-5D values.

Have Any Potential Significant and Substantial Health-Related Benefits Been Identified That Were Not Included in the Economic Model, and How Have They Been Considered?

The Committee concluded that some adverse effects of oral corticosteroid use, such as obesity, hypertension, mood changes, depression, psychosis, thinning skin, delayed wound healing, reduced growth in children, and increased risk of infection were additional important factors that had not been captured when calculating the quality-adjusted life years (QALY).

The Committee concluded that the potential additional health-related benefits conferred to carers as a result of omalizumab use could not currently be quantified.

Are There Specific Groups of People for Whom the Technology Is Particularly Cost-Effective?

The Committee noted that the base-case incremental cost-effectiveness ratio (ICERs) in the overall population of adults, adolescents, and children were similar across the 3 high-risk populations, ranging from £32,200 to £33,200 per QALY gained without incorporating the patient access scheme for omalizumab.

What Are the Key Drivers of Cost-Effectiveness?

The key drivers of cost effectiveness were the asthma-related mortality rates, the degree to which omalizumab improves health-related quality of life, and, for people who take maintenance oral corticosteroids, whether or not the model included adverse effects from oral corticosteroids.

Most Likely Cost-Effectiveness Estimate (Given as an ICER)

The Committee concluded that the most plausible ICER was £23,200 per QALY gained for the combined population of adults, adolescents, and children on continuous or frequent courses of oral corticosteroids, defined as 4 or more courses in the year before receiving omalizumab incorporating the patient access scheme for omalizumab.

Method of Guideline Validation

External Peer Review

Description of Method of Guideline Validation

Consultee organisations from the following groups were invited to comment on the draft scope, Assessment Report and the Appraisal Consultation Document (ACD) and were provided with the opportunity to appeal against the Final Appraisal Determination.

- Manufacturer/sponsors
- Professional/specialist and patient/carer groups
- Commentator organisations (without the right of appeal)

In addition, individuals selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups were also invited to comment on the ACD.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

The Appraisal Committee considered clinical and cost-effectiveness evidence and a review of this evidence by the Technology Assessment Group. For clinical effectiveness, randomised controlled trials were the main source of evidence. For cost-effectiveness, the Assessment Group reviewed published cost analyses as well as an economic model submitted by the manufacturer.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate use of omalizumab for the treatment of severe persistent allergic asthma in people aged 6 years and over

Potential Harms

The summary of product characteristics lists injection site pain, swelling, erythema and pruritus, and headaches as the most commonly reported adverse reactions for omalizumab treatment in adults and adolescents. The most commonly reported adverse reactions for omalizumab treatment in children are headaches, pyrexia, and upper abdominal pain.

For the full details of adverse events and contraindications, see the summary of product characteristics available at http://emc.medicines.org.uk/ .

Qualifying Statements

Qualifying Statements

- This guidance represents the views of the National Institute for Health and Care Excellence (NICE) and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.
- Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

Implementation of the Guideline

Description of Implementation Strategy

- Section 7(6) of the National Institute for Health and Care Excellence (NICE) (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, National Health Service (NHS) England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- When NICE recommends a treatment 'as an option', NHS must make sure it is available within the period set out in the paragraph above. This means that, if a patient has severe persistent confirmed allergic immunoglobulin E (IgE)-mediated asthma and the doctor responsible for their care thinks that omalizumab is the right treatment, it should be available for use, in line with NICE's recommendations.
- The Department of Health and the manufacturer have agreed that omalizumab will be available to the NHS with a patient access scheme, which makes omalizumab available with a discount. The size of the discount is commercial in confidence. It is the responsibility of the manufacturer to communicate details of the discount to the relevant NHS organisations. Any enquiries from NHS organisations about the patient access scheme should be directed to the Commercial Operations Team at Novartis Pharmaceuticals UK on 01276 698717 or via email to commercial.team@novartis.com.
- NICE has developed a tool to help organisations put this guidance into practice (listed below). This tool is available on the NICE Web site .
    - A costing statement explaining the resource impact of this guidance

Implementation Tools

Patient Resources

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

National Institute for Health and Care Excellence (NICE). Omalizumab for treating severe persistent allergic asthma (review of technology appraisal guidance 133 and 201). London (UK): National Institute for Health and Care Excellence (NICE); 2013 Apr. 64 p. (Technology appraisal guidance; no. 278).

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2007 Nov (revised 2013 Apr)

Guideline Developer(s)

National Institute for Health and Care Excellence (NICE) - National Government Agency [Non-U.S.]

Source(s) of Funding

National Institute for Health and Care Excellence (NICE)

Guideline Committee

Appraisal Committee

Composition of Group That Authored the Guideline

Committee Members: Dr Amanda Adler (*Chair*), Consultant Physician, Addenbrooke's Hospital; Professor Ken Stein (*Vice Chair*), Professor of Public Health, Peninsula Technology Assessment Group (PenTAG), University of Exeter; Dr Ray Armstrong, Consultant Rheumatologist, Southampton General Hospital; Dr Jeff Aronson, Reader in Clinical Pharmacology, University Department of Primary Health Care, University of Oxford; Dr Peter Barry, Consultant in Paediatric Intensive Care, Leicester Royal Infirmary; Professor John Cairns, Professor of Health Economics Public Health and Policy, London School of Hygiene and Tropical Medicine; Dr Mark Chakravarty, External Relations Director - Pharmaceuticals & Personal Health, Oral Care Europe; Mark Chapman, Health Economics and Market Access Manager, Medtronic UK; Professor Fergus Gleeson, Consultant Radiologist, Churchill Hospital, Oxford; Eleanor Grey, Lay member; Professor Jonathan Grigg, Professor of Paediatric Respiratory and Environmental Medicine, Barts and the London School of Medicine and Dentistry, Queen Mary University London; Sanjay Gupta, Young physically disabled (YPD) Service Case Manager, Southwark Health and Social Care, Southwark PCT; Professor Daniel Hochhauser, Consultant in Medical Oncology; Dr Neil Iosson, General Practitioner; Anne Joshua, Associate Director of Pharmacy, NHS Direct; Terence Lewis, Lay Member; Professor Ruairidh Milne, Director of Strategy and Development and Director for Public Health Research at the National Institute for Health Research (NIHR) Evaluation, Trials and Studies Coordinating Centre at the University of Southampton; Dr Rubin Minhas, General Practitioner and Clinical Director, BMJ Evidence Centre; Dr Elizabeth Murray, Reader in Primary Care, University College London; Dr Peter Norrie, Principal Lecturer in Nursing, DeMontfort University; Dr Sanjeev Patel, Consultant Physician & Senior Lecturer in Rheumatology, St Helier University Hospital; Dr John Pounsford, Consultant Physician, Frenchay Hospital, Bristol; Dr Danielle Preedy, Lay Member; Dr John Rodriguez, Assistant Director of Public Health, NHS Eastern and Coastal Kent; Alun Roebuck, Consultant Nurse in Critical and Acute Care, United Lincolnshire NHS Trust; Roderick Smith, Finance Director, West Kent Primary Care Trust; Cliff Snelling, Lay Member; Marta Soares, Research Fellow, Centre for Health Economics, University of York; Professor Andrew Stevens, Professor of Public Health, Department of Public Health and Epidemiology, University of Birmingham; David Thomson, Lay Member; Tom Wilson, Director of Contracting & Performance, NHS Tameside & Glossop

Financial Disclosures/Conflicts of Interest

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

Guideline Status

This is the current release of the guideline.

This guideline updates two previous versions:

- National Institute for Health and Clinical Excellence (NICE). Omalizumab for the treatment of severe persistent allergic asthma in children aged 6 to 11 years. London (UK): National Institute for Health and Clinical Excellence (NICE); 2010 Oct. 38 p. (Technology appraisal guidance; no. 201).
- National Institute for Health and Clinical Excellence (NICE). Omalizumab for severe persistent allergic asthma. London (UK): National Institute for Health and Clinical Excellence (NICE); 2007 Nov. 28 p. (Technology appraisal guidance; no. 133).

Guideline Availability

Electronic copies: Available from the National Institute for Health and Care Excellence (NICE) Web site .

Availability of Companion Documents

The following is available:

- Omalizumab for treating severe persistent allergic asthma (review of technology appraisal guidance 133 and 201). Costing statement. London (UK): National Institute for Health and Care Excellence (NICE); 2013 Apr. 6 p. (Technology appraisal 201). Electronic copies: Available in Portable Document Format (PDF) from the National Institute for Health and Care Excellence (NICE) Web site .
- Omalizumab for the treatment of severe persistent allergic asthma: a systematic review and economic evaluation. Technology Assessment Report. Centre for Reviews and Dissemination (CRD)/Centre for Health Economics (CHE); 2012 Apr. 355 p. Electronic copies: Available in PDF from the NICE Web site .

Patient Resources

The following is available:

- Omalizumab for severe persistent allergic asthma. Information for the public. London (UK): National Institute for Health and Care Excellence (NICE); 2013 Apr. 6 p. Electronic copies: Available in Portable Document Format (PDF) from the National Institute for Health and Care Excellence (NICE) Web site .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

This NGC summary was completed by ECRI Institute on May 26, 2011. This NGC summary was updated by ECRI Institute on June 14, 2013. This summary was updated by ECRI Institute on November 14, 2014 following the U.S. Food and Drug Administration advisory on Xolair (omalizumab).

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